REMARKS

Claims 1, 3-43, 50-55 and 61-66 were pending in this application. By this amendment, applicants have amended claims 1, 19, 25-31, 43, 50-54, 61 and 66 and added claims 67-74. Applicants have also canceled claim 36 without disclaimer or prejudice to applicants' rights to pursue the subject matter of this claim in this or another application. Finally, applicants have added new claims 67-74. Accordingly, claims 1, 3-35, 37-43, 50-55 and 61-74 are under examination in this application.

Support for the amendment to claim 19 may be found, *inter alia*, on page 7, lines 28-33 of the subject specification.

Support for the amendments to claims 1, 25-31, 43 and 50-54 may be found, *inter alia*, on page 1, lines 18-20 of the subject specification.

Support for the amendment to claim 61 may be found, *inter alia*, on page 7, line 25-26 of the subject specification.

Support for the amendment to claim 66 may be found, *inter alia*, on page 9, line 23-24 of the subject specification.

Support for new claims 67-74 may be found, *inter alia*, on page 10, lines 3-17 and Page 12, lines 11 to 35 of the subject specification.

Sixth Supplemental Information Disclosure Statement

Applicants note that the Examiner crossed out six citations on the PTO Form-1449 submitted with their July 2, 2002 Information Disclosure Statement instead of initialing these citations to indicate that they have been considered in the subject application. A copy of sheet 3 of the above mentioned PTO Form-1449 showing the items crossed out by Examiner is attached hereto as **Exhibit A**. Similarly, the Examiner also crossed out four citations on the PTO Form-1449 submitted with applicants' August 1, 2002 Information Disclosure Statement. A copy of sheet 1 of the August 1, 2003 PTO Form-1449 is attached hereto as **Exhibit B**. All ten crossed out citation references were U.S. Patent Applications which were all unpublished at the times of submission.

Applicants point out that 37 C.F.R. § 1.98(a)(1) makes it clear that an Information Disclosure Statement must include "a list of all patents, publications, applications, or other information submitted for consideration by the office" (emphasis added). In addition, applicants draw the Examiner's attention to M.P.E.P. 609, entitled "Information Disclosure Statement," Section III (A)(1) which states in part

> . . . U.S. applications must be identified by the inventor, the eight digit application number (the two digit series code and the six digit serial number), and the filing date . . . A separate list is required so that it is easy to confirm that applicant intends to submit an Information Disclosure Statement and because it provides a readily available checklist for the Examiner to

> indicate which identified documents have been considered . . . Use of either form PTO-1449 . . . to list the documents is encouraged (emphasis added).

Accordingly, pursuant to 37 C.F.R. § 1.98(a)(1) and to M.P.E.P. § 609, pending U.S. applications are to be disclosed in Information Disclosure Statements and are to be considered by the Examiner. The Examiner should then "indicate which documents have been considered" on Form PTO-1449.

However, since their initial submission, seven of the U.S. applications have become U.S. application publications or been issued as a U.S. patent. Two of the seven items were included in a Supplemental Information Disclosure Statement submitted by the applicants on July 15, 2003. These items are:

1. U.S. Patent Publication No. US-2002-0037848-A1, published March 28, 2002 (Eisenbach-Schwartz et al.), previously listed as U.S. Serial No. 09/765,301;

2. U.S. Patent Publication No. US-2003-0004099-A1, published January 2, 2003 (Eisenbach-Schwartz et al.), previously listed as U.S. Serial No. 09/765,644.

A copy of the PTO Form-1449 submitted on July 15, 2003 listing these items is included herewith as **Exhibit C** and an indication of the consideration of these references is again requested.

The remaining five U.S. application publications are listed below and are submitted herewith as **Exhibits 1-5** for the Examiner's review. Furthermore, the three remaining unpublished U.S. applications are resubmitted as **Exhibits 6-8**

for the Examiner's review. The Examiner is requested to review each of these ten references and initial next to the citation of each on the PTO Form-1449 submitted herewith as **Exhibit D** and return a copy of same to applicants with the Examiner's next communication regarding this application.

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following publications which are listed again on the attached Form PTO-1449 **(Exhibit D)** and copies of References 1-8 are attached hereto as **Exhibits 1-8.**

1. U.S. Patent No. 6,514,938 B1 issued February 3, 2003 (Gad et al.), previously listed at U.S. Serial No. 09/405,743 **(Exhibit 1)**;

2. U.S. Patent Application Publication No. US-2002-0055456-A1, published May 9, 2002 (Aharoni et al.), previously disclosed as U.S. Serial No. 09/768,872 **(Exhibit 2)**;

3. U.S. Patent Application Publication No. US-2002-0115103-A1, published August 22, 2002 (Gad et al.), previously disclosed as U.S. Serial No. 09/816,989 **(Exhibit 3)**;

4. U.S. Patent Application Publication No. US-2002-0077278-A1, published June 20, 2002 (Yong and Chabot et al.), previously disclosed as U.S. Serial No. 09/875,429 **(Exhibit 4)**;

5. U.S. Patent Application Publication No. US-2002-0182210-A1, published December 5, 2002 (Rodriguez and

Ure et al.), previously disclosed as U.S. Serial No. 09/885,227 (**Exhibit 5**);

6. U.S. Serial No. 09/359,099, filed July 22, 1999 (Strominger, et al.)(**Exhibit 6**);

7. U.S. Serial No. 09/487,793, filed January 20, 2000 (Eisenbach-Schwartz et al.)(**Exhibit 7**);

8. U.S. Serial No. 09/620,216, filed July 20, 2000 (Eisenbach-Schwartz et al.)(**Exhibit 8**).

No fee is believed due with the submission of this Supplemental Information Disclosure Statement since all items were previously submitted prior to mailing of the first office action on the merits.

Withdrawal of Claim 55

In Section 1 of the July 31, 2003 Office Action, the Examiner withdrew claim 55 from consideration.

In response, applicants contend the withdrawal of claim 55 is improper. There is no additional burden for the examination of claim 55 since this claim contains the limitations of claim 50 which the examiner has found to be within the invention elected by the applicants.

Moreover, applicants point out that claim 50 is a linking claim which links the process of making claims, e.g. claim 43, and use claims, e.g. claim 55. Applicants draw the Examiner's attention to M.P.E.P. Section 809 which states, in part,

> **The linking claims must be examined with the invention 1 ct d, and** should any linking claim be allowed, the restriction requirement must be withdrawn. Any claim(s) directed to the nonelected invention(s), previously withdrawn from consideration, which depends from or includes all the limitations of the allowable linking claim must be rejoined and will be fully examined for patentability. (Emphasis added)

Applicants also draw the Examiner's attention to M.P.E.P. Section 809.03 which states in part

> The most common types of linking claims which, if allowed, act to prevent restriction between inventions that can otherwise be shown to be divisible are...(D) a claim to the product linking a process of making and a use(process of using).

Consequently, Applicants maintain that claim 55 should be examined together with claim 50 from which it depends. Regardless, when linking claim 50 is found to be allowable, claim 55 will need to be rejoined and fully examined for patentability.

Applicants also note that similar comments are applicable to new claims 67-74.

Rejections under 35 U.S.C. § 112

In Section 3 of the July 31, 2003 Office Action, the Examiner has rejected claim 36 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner alleged that the claim(s) contains

subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner alleged that claim 36 recites that the pharmaceutical composition is in an aqueous form. However, the Examiner alleged that the claim is dependent upon claim 32, which is dependent upon claim 1. The Examiner alleged that claim 1 recites that the composition comprises both copolymer-1 and microcrystalline cellulose. The Examiner alleged that Microcrystalline cellulose is a well known in the art as a stable and physiologically inert exipient for solid compositions such as tablets, not for liquid formulations. The Examiner alleged that the specification discloses the formulation and use of copolymer-1 in solution at page 10, lines 19-27 and Example 2, for example. However, the Examiner alleged that the specification discloses only the formulation of copolymer-1 into the solution and does not disclose the addition of microcrystalline cellulose to said solution. Accordingly, the Examiner alleged that there is no written description of a solution or liquid form of the pharmaceutical composition comprising both copolymer-1 and microcrystalline cellulose.

In response, applicants have canceled claim 36.

In Section 4 of the July 31, 2003 Office Action, the Examiner rejected claims 19, 61 and 66 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner alleged that claim 19 recites the limitation "said enteric coating" in line 2. The Examiner alleged that there is no antecedent basis for this limitation in the claim. The Examiner alleged that there is no support for the recitation in base claim 1. The Examiner suggested that applicant should amend the claim to be dependent upon claim 18, which contains the proper antecedent basis.

In response, applicants have amended claim 19 to depend on claim 18.

The Examiner alleged that claim 61 is indefinite in the recitation of "protase inhibitor." The Examiner alleged that it is suggested that the claim be amended to recite -protease inhibitor--.

In response, applicants have amended claim 61 to recite "protease inhibitor."

The Examiner alleged that claim 66 is indefinite in that it is dependent upon a canceled claim. The Examiner alleged that applicant should amend the claim to be dependent upon claim 65, which contains the proper antecedent basis.

In response, applicants have amended claim 66 to depend on claim 65.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §1.112, second paragraph.

Non-statutory Double Patenting Rejection

In Section 5 of the July 31, 2003 Office Action, The Examiner rejected claims 1, 3-43, 50-54 and 62, 63 and 65 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 7-14 of U.S. Patent No. 6,214,791 to Arnon et al (on form PTO-1449 filed July 8, 2002 - courtesy copy filed May 5, 2003)("the '791 patent") in view of U.S. Patent No. 6,024,981 to Khankari et al (A on form PTO-892)("the '981 patent")

Specifically, the Examiner alleged that claims 7-11 of the '791 patent are drawn to the use of copolymer-1 for the manufacture of a medicament or pharmaceutical composition for the treatment of multiple sclerosis via ingestion or inhalation (7), wherein the medicament comprises 0.1-1000 mg of copolymer-1 (8), is formulated for oral or nasal administration (9), is administered via inhalation (10), or is enterically coated (11). Claim 7 of the '791 patent is a genus claim which broadly encompasses the presently claimed method of making a copolymer-1 medicament in light of the disclosure of the '981 patent [Instant claims 43 and 64-65]. The Examiner alleged that claims 12-14 of the '791 patent are drawn to a pharmaceutical composition for the treatment of multiple sclerosis via ingestion or inhalation (12), wherein the pharmaceutical composition is in solid, liquid, aerosol or inhalable powder form (13), or is enterically coated (14). The Examiner alleged that claim 12 of the '791 patent is a genus claim which broadly encompasses the presently claimed pharmaceutical composition in light of the further disclosure of the '791 patent and the disclosure of the '981 patent.

The Examiner alleged that the pharmaceutical composition recited in claim 12 of the '791 patent comprises as an active ingredient a therapeutically effective amount of Copolymer

1(glatimer acetate). The Examiner alleged that, as is evidenced by the disclosure of the '791 patent, the composition is used to treat multiple sclerosis by oral administration of copolymer-1 through ingestion, and that when copolymer-1 is introduced orally it may be in solid form, and it may be mixed with pharmaceutically acceptable carrier. The Examiner alleged that the disclosure of the '791 patent indicates that the use of enteric coatings is well known in the art, including methacrylic acid copolymer (Eudragit L; column 3, lines 27-42 in particular)[Instant claims 18, 20, 29-31]. The Examiner alleged that the '791 patent further discloses that the administration of the composition orally, nasally or bronchially in liquid or solid form with a range of copolymer-1 from 0.1 to 1000 mg (column 2, line 45 to column 3, line 26) [claims 23-28, 32-42, 50-54, 62-63].

The Examiner acknowledged that the '791 patent does not specifically recite that the carrier is microcrystalline cellulose or admixture with a lubricant.

The Examiner alleged that microcrystalline cellulose is well known in the art as a stable and physiologically inert exipient. The Examiner alleged that the '981 patent teaches that microcrystalline cellulose is a non-effervescent wicking or disintegration agent for solid compositions such as tablets (column 13, lines 47-59 in particular) and that tablets can be made in unit dosage forms adapted for oral administration (column 4, lines 30-35). The Examiner alleged that the '981 patent teaches that the percentage of active ingredient, and therefore of the carrier in proportion to that active ingredient, in a solid pharmaceutical preparation may be selected according to known principals of pharmacy (column 5, lines 12-14 in particular). The Examiner alleged that the '981

patent teaches that the active ingredient used can vary greatly and is generally provided in an amount between greater than zero and 80% (column 5, lines 34-56 in particular). The Examiner alleged that the '981 patent teaches that a typical range for a disintegrant such as microcrystalline cellulose is conventionally as high as 20% but can be increased for rapidly disintegrating dosage forms (column 13, lines 60-67 in particular)[Instant claims 1, 3-8]. The Examiner alleged that the '981 patent also teaches modified starches as a disintegration agent (column 13, lines 47-59 in particular)[Claims 8-14]. The Examiner alleged that the '981 patent further teaches lubricants, including magnesium stearate (column 10, lines 13-51 in particular)[claims 15-17]. The Examiner alleged that claims 34-35 are included because the use of preservatives in pharmaceutical formulations is well known to enhance the longevity of the formulation in storage.

Accordingly, the Examiner alleged that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to manufacture a composition comprising copolymer-1 as recited in claims 7-14 of the '791 patent using the well-known microcrystalline cellulose as an exipient and magnesium stearate as a lubricant, optimizing the proportions of active ingredient as taught by the '981 patent.

In Section 6 of the July 31, 2003 Office Action, the Examiner rejected claims 1, 20, 21, 22, 43 and 64 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 7-14 of the '791 patent in view of the '981 patent and U.S. Patent No. 5,965,600 to Sato et al (B on form PTO-892)("the '600 patent"). The Examiner referred the applicants to the discussion of the '791 and '981

patents supra.

The Examiner acknowledged that the combined disclosures do not specifically recite film coating of the solid form in combination with the enteric coating.

The Examiner alleged that the '600 patent teaches a medicament in tablet form comprising both an enteric coating and a film coating, which could be polyvinyl alcohol (column 4, lines 39-62 in particular). The Examiner alleged that it would have been *prima facie* obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings of the '600 patent with the combined disclosures of the '791 and '981 patents. The Examiner alleged that one would have been motivated to combine the references with a reasonable expectation of success by the teaching of the '600 patent that multiple coatings of a tablet including both enteric and film coatings is "customary" in the art.

In Section 7 of the July 31, 2003 Office Action, the Examiner rejected claims 1 and 61 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 12-14 of the '791 patent in view of the '981 patent and U.S. Patent No. 6,162,800 to Dolle et al (C on form PTO-892)("the '800 patent"). The Examiner referred the applicants to the discussion of the '791 and '981 patents *supra*.

The Examiner acknowledged that the combined disclosures do not specifically recite protease inhibitors in a medicament for multiple sclerosis.

The Examiner alleged that the '800 patent teaches a

pharmaceutical composition comprising a protease inhibitor for the treatment of IL-1P mediated disease states (column 7, lines 39-56 in particular). The Examiner alleged that it would have been *prima facie* obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings of the '800 patent with the combined disclosures of the '791 and '981 patents. The Examiner alleged that one would have been motivated to combine the references with a reasonable expectation of success by the teaching of the '800 patent that multiple sclerosis is an IL-1p mediated disease state which can be treated with medicaments comprising a protease inhibitor.

In Section 8 of the July 31, 2003 Office Action, the Examiner rejected claims 43, 65 and 66 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 7-11 of the '791 patent in view of the '981 patent and U.S. Patent No. 4,129,666 to Wizerkaniuk (D on form PTO-892)("the '666 patent"). The Examiner referred the applicants to the discussion of the '791 and '981 patents supra.

The Examiner alleged that the combined disclosures do not specifically recite the use of a rotating pan for application of the enteric coating to the solid form of the pharmaceutical composition.

The Examiner alleged that the '666 patent teaches the application of enteric coating medicinal pellets with an enteric coating using a rotating pan apparatus (entire patent). The Examiner alleged that it would have been *prima facie* obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings of

the '666 patent with the combined disclosures of the '791 and '981 patents. The Examiner alleged that one would hav been motivated to combine the references with a reasonable expectation of success by the teaching of the '666 patent that methods of applying an enteric coating such as spraying requires the use of solvents which may be toxic, while the rotating pan method does not require such solvents (column 1, lines 24-56 in particular).

In response to the obviousness-type double patenting rejections set forth in Sections 5-8 of the July 31, 2003 Office Action, applicants respectfully direct the Examiner to their remarks below, which address the obviousness-type double patenting rejections together with the rejections under 35 U.S.C. § 103 because both rejections are premised on the same combinations of references.

Claim Rejections under 35 U.S.C. § 103

In Section 10 of the July 31, 2003 Office Action, the Examiner rejected claims 1, 3-43, 50-54 and 62, 63 and 65 under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,214,791 (on form PTO-1449 filed July 8, 2002 - courtesy copy filed May 5, 2003) or WO 98/30227 (on form PTO-1449 filed July 8, 2002 - courtesy copy filed May 5, 2003)("the '227 publication"), in view of the '981 patent.

The Examiner referred the applicants to the discussion of the '791 patent supra, which is the U.S. national stage of WO 98/30227.

The Examiner alleged that the '227 publication (and the '791 patent which corresponds thereto) teaches a pharmaceutical

composition comprising as an active ingredi nt a therapeutically effectiv amount of Copolymer 1 (glatimer acetate). The Examiner's allegation of what the '227 publication teaches is identical to the Examiner's allegation of what the '791 patent teaches, and which are summarized above on pages 19-20 of this response.

The Examiner alleged that microcrystalline cellulose is well known in the art as a stable and physiologically inert exipient. See the Examiner's alleged teachings of the '981 patent presented on pages 20-21 above.

In Section 11 of the July 31, 2003 Office Action, the Examiner rejected claim 61 under 35 U.S.C. § 103(a) as allegedly unpatentable over the '791 patent or the '227 publication, either in view of the '981 patent as applied to claim 1 above, and further in view of U.S. Patent No. 6,162,800 ("the '800 patent.")

The Examiner's comments about and alleged teachings of the '800 patent are presented above on page 22-23.

In Section 12 of the July 31, 2003 Office Action, the Examiner rejected claims 65 and 66 under 35 U.S.C. § 103(a) as allegedly unpatentable over the '791 patent or the '227 publication, either in view of the '981 patent as applied to claims 1 and 43 above, and further in view of the '666 patent.

The Examiner's comment about and alleged teachings of the '666 patent are presented above on pages 23-24.

In Section 13 of the July 31, 2003 Office Action, the Examiner rejected claims 21, 22 and 64 under 35 U.S.C. § 103(a) as

allegedly unpatentable ov r U.S. Patent No. 6,214,791 (on form PTO-1449 filed July 8, 2002 - courtesy copy filed May 5, 2003) or the '227 publication, either in view of the '981 patent as applied to claims 1, 20 and 43 above, and further in view of U.S. Patent No. 5,965,600 to the '600 patent.

The Examiner's comments about and alleged teachings of the '600 patent are presented above on pages 21-22.

Applicants' Response to the Non-statutory Double Patenting Rejections and the Rejections under 35 U.S.C. § 103

In response to the non-statutory double patenting rejections and to the rejections under 35 U.S.C. § 103, applicants point out that claim 1 recites "an amount of microcrystalline cellulose in excess of 50 % by weight of the composition." None of the Examiner's cited references teach or suggest making a pharmaceutical composition which comprises "in excess of 50 %" microcrystalline cellulose by weight. As disclosed on page 37, lines 17-32, the use of in excess of 50 % microcrystalline cellulose by weight results in pharmaceutical compositions with excellent flow and mixing characteristics, improved dissolution and improved stability over that which would have been expected based on the properties of glatiramer acetate. Indeed, as discussed on page 38, lines 1-13 of the subject specification, based on the properties of glatiramer acetate, it was unexpected that the formulation with microcrystalline cellulose, particularly in excess of 50 %, would have any, much less significantly, improved pharmaceutical properties suitable for oral administration.

Use of microcrystalline cellulose, at any amount, in a formulation with glatiramer acetate is neither disclosed nor suggested in the prior art. As the Examiner has admitted, the

'791 patent does not disclose th use of microcrystalline cellulose with glatiramer acetate. Moreover, as discussed herein, applicants' use of microcrystalline cellulose in excess of 50% with glatiramer acetate makes the current invention patentable over all of the cited prior art.

For example, the claimed formulation has an advantageous property in that it allows for matching *in vitro* dissolution profiles of the 5 mg glatiramer acetate and the 50 mg glatiramer acetate tablets weight as shown in Figure 3. Specifically, and unexpectedly, even though the 50 mg glatiramer acetate tablet is four times the weight of the 5 mg glatiramer acetate tablet, the tablets have similar dissolution profiles. (page 37, line 29 to page 38, line 13). It is unexpected based on the prior art that the use of microcrystalline cellulose or in excess of 50 % by weight microcrystalline cellulose will produce such advantageous properties in the pharmaceutical compositions of the subject invention.

Since the Examiner has cited the same references in support of the obviousness-type double patenting rejection as he cited in support of the 35 U.S.C. § 103(a) rejection, the applicants' comments regarding both rejections are grouped together below according to the references cited.

<u>Rejection of Claims 1-35, 37-43, 50-54, and 61-66 over the'791 patent or the '227 publication in view of the '981 patent</u>

As the Examiner had acknowledged, the '791 patent does not teach or disclose the use of microcrystalline cellulose with glatiramer acetate formulations. Although the '981 patent does disclose microcrystalline cellulose as a non-effervescent disintegrant, 1) it is disclosed as one among several

disintegrants, 2) it is not suggested for use with glatiramer acetate and 3) the amount of microcrystalline cellulose used is far lower than applicants are claiming in the subject application.

First, the '981 patent discloses the use of other non-effervescent disintegration agents besides microcrystalline cellulose (Column 13, lines 48-59). No motivation is of record for selecting microcrystalline cellulose for use with glatiramer acetate as opposed to any of the other disintegration agents listed in the '981 patent. Applicants' selection of the use of microcrystalline cellulose with glatiramer acetate should be sufficient to indicate patentability of applicants' claims.

Second, the non-obviousness of applicants' claimed selection is apparent upon review of the examples of active ingredients in the '981 patent which are formulated with the disintegration agents. The examples given are all relatively small molecules with molecular weights less that 2000 Daltons (Column 4, lines 35-65). On the other hand, glatiramer acetate has a molecular weight of between 4700 and 11,000 Daltons. Therefore, due to the difference in the size of the molecules involved, it would not be obvious to one skilled in the art that microcrystalline cellulose would be an effective disintegration agent when combined with glatiramer acetate. It would certainly not be obvious to combine glatiramer acetate with microcrystalline cellulose at concentration in excess of 50%. In fact, the '981 patent discloses the concentration of the active ingredient can go as high as 80% (Column 5, lines 34-46) thus suggesting a limit of less than 20% on disintegration agent concentration. This further renders the use of in excess of 50% microcrystalline cellulose

in combination with glatiramer ac tate non-obvious.

Finally, the '981 patent contemplates microcrystalline cellulose as high as 20% but teaches the range is normally 2-5%. According to the preferred embodiment of the '981 patent the concentration of microcrystalline cellulose ranges only as high as 12% (Column 13, line 60 to column 14, line 6). In fact, the '981 patent teaches away from the use of higher concentrations of disintegrants in general and microcrystalline cellulose specifically. In the first 8 examples cited in the '981 patent, microcrystalline cellulose was either not used or present at the level of only 2%. Other disintegrants (sometimes called wicking agents) were also used but never at levels above 6%. Therefore, in these examples the total disintegrant content was 8% or less (Column 15, line 51 to column 19, line 5). All of these examples were highlighted for the rapid dissolution of the tablet and satisfaction with the feel of the dissolved tablet in the mouth. The '981 patent also teaches away from the use of higher concentrations of disintegrants and microcrystalline cellulose in Examples 9 and 10 (Column 19, lines 6-44). In Example 9, the total disintegrant content is 89 mg per 1100 mg tablet or 8.1%. In Example 10, the microcrystalline cellulose content was 90 mg per 990 mg tablet or 9.1%. In both these examples, the tablets were found to dissolve slower and tasted terrible to the patients. The '981 patent then attributes these negative characteristics to higher concentrations of disintegrants and then asserts the advantage of its invention as the use of lower levels of these materials. "Finally, the content in the matrix both in terms of direct versus non-direct compression material, as well as the percentage of disintegrants used in accordance with the Cousins et al formulation, were considerably higher adding to the unpleasant

gritty feel of th disintegrated formulation. The invention minimizes this and, where possible, th only grittin ss is a result of the coated active material and a relatively minor percentage of other excipients" (Column 19, lines 45-67). Therefore, one would not be motivated by the '981 patent to prepare a formulation with in excess of 50% microcrystalline cellulose. In fact, one skilled in the art would be discouraged from attempting such a formulation after reading the '981 patent.

As stated above, applicants have obtained an effective glatiramer acetate formulation with microcrystalline cellulose in excess of 50% by weight. One skilled in the art would not have been motivated to use a microcrystalline cellulose level of in excess of 50% with glatiramer acetate based on the disclosure of the '981 patent, or the prior art generally. Indeed, no motivation is of record for increasing the level of this rather expensive ingredient to over 2.5 times its highest recommended level of 20%.

Applicants maintain that Claims 1 and 29 are novel and non-obvious over the '791 in light of the '981 patent since the '791 patent does not disclose the use of microcrystalline cellulose with glatiramer acetate and the '981 patent neither teaches nor suggests the use of microcrystalline cellulose at levels of in excess of 20% with glatiramer acetate. Therefore, applicants respectfully request that the Examiner withdraw the rejections of claims 1 and 29 based on obvious-type double patenting and obviousness since these claims recite levels of microcrystalline cellulose of in excess of 50%. Moreover, claims 2-28, 30-35, 37-43, 50-54, and 61-66 all depend directly or indirectly on either claim 1 or claim 29 and further limit the independent claims to yet higher

levels of microcrystalline cellulose. Accordingly, the Examiner is also requested to withdraw the obvious-type double patenting and obviousn ss rejections of the dependent claims on additional grounds.

Furthermore, the '227 publication is the PCT application from which arose the national stage U.S. application that became the '719 patent. As expected, like the '791 patent, the '227 publication discloses a treatment for multiple sclerosis using glatiramer acetate. Like the '791 patent, the '227 publication does not disclose the use of microcrystalline cellulose with glatiramer acetate. As discussed above regarding the '791 patent, the '227 publication when combined with the '981 patent does not make the subject application's invention obvious to one skilled in the art because the '981 patent does not teach or suggest the use of microcrystalline cellulose at levels greater than 50% with glatiramer acetate. Therefore, applicants respectfully request that the Examiner withdraw his rejections of claims 1, 3-35, 37-43, 50-54, 62-63 and 65 based on obviousness over the '791 and the '227 publication in light of '981 patent for the reasons discussed above.

Rejection of Claims 1, 20, 21, 22, 43 and 64 over the '791 patent or the '227 publication in view of the '981 and '600 patents

The applicants agree with the Examiner that the '791 and '981 patents do not disclose the use of a film coating in combination with an enteric coating. However, the combination of this '791 and '981 patents with the '600 patent does not make obvious to one skilled in the art a tablet containing the combination of glatiramer acetate, greater than 50% microcrystalline cellulose, a film coating and an enteric

coating. Therefore, applicants respectfully request that the Examiner withdraw the rejection of claims 1, 20, 21, 22, 43 and 64 based on obvious-type double patenting over the '791 patent in light of the '981 and '600 patents.

Similarly, the obviousness rejection fails when considering the '227 publication in light of the '981 and '600 patents.

Rejection of Claims 1 and 61 over the '791 patent or '227 publication in view of the '981 and '800 patents

Since, as the Examiner has stated, the '791 and '981 patents do not teach the use of protease inhibitors in a medicament for multiple sclerosis and since '800 patent contains no disclosure teaching or suggesting combining a protease inhibitor with glatiramer acetate and microcrystalline cellulose in excess of 50%, applicants maintain that the invention claimed in claims 1 and 61 is novel and not obvious to one skilled in the art. Therefore, applicants respectfully request that the Examiner withdraw the rejection of claims 1 and 61 based on obvious-type double patenting over the '791 and '981 patents in light of the '800 patent.

Similarly, the obviousness rejection fails when considering the '227 publication with the '981 and '800 patents.

Rejection of Claims 43, 65 and 66 over the '791 patent or '227 publication in view of the '981 and '666 patents

While the applicants agree with the Examiner's assessment that the '666 patent discloses a method of applying an enteric coating using a rotating pan method, the applicants maintain that this reference when combined with the '791 patent or the '227 publication and the '981 patent would not make the subject invention obvious to one skilled in the relevant art.

None of these references individually or in combination teach or suggest treating multiple scl rosis with glatiramer acetate combined with microcrystalline cellulose in excess of 50% and with an enteric coating applied by the rotating pan method. Therefore, the applicants request that the Examiner withdraw the obviousness-type double patenting rejection of claims 43, 65 and 66 over '791 patent in light of the '981 and '666 patents and his obviousness rejection of claims 65 and 66 over the '227 publication in light of the '981 and '666 patents.

For all of the above reasons, applicants respectfully request that the Examiner withdraw the rejection under non-statutory obviousness-type double patenting and 35 U.S.C. § 103.

Common Ownership of the '791 patent and the subject application

The Examiner reminded the applicants that the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). The Examiner stated that commonly assigned U.S. Patent No. 6,214,791, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. The Examiner also stated that, in order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. § 103(c) and 37 CFR § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. The Examiner further stated that failure to comply with this requirement will result in a holding of abandonment

of the application.

The Examiner inform d the applicants that a showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g), or 35 U.S.C. § 102(e) for applications filed on or after November 29, 1999.

In response, applicants point out that the '791 patent issued from an application which was the U.S. national stage application of PCT International Application No. PCT/US98/00375 which published as the '227 publication. As the Examiner is aware, the '227 publication and the subject application are both assigned to Yeda Research and Development Co. Ltd. The assignment document assignment the '227 publication to Yeda Research and Development Co. Ltd. is dated March 26, 1998, and a copy is attached hereto as **Exhibit E.** The subject application was filed almost two years later on February 16, 2000 and for the convenience of the Examiner a copy of the Assignment document in the subject application is attached as **Exhibit F.**

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Gary J. Gershik

John P. White
Registration No. 28,678
Gary J. Gershik
Registration No. 39,992
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Gary J. Gershik 10/30/03

John P. White Date
Reg. No. 28,678
Gary J. Gershik
Reg. No. 39,992

Form PTO-1449 U.S. Department of Commerce Patent and Trademark Office

Atty. Dock. No.	Serial No.
606 A	09/788,131
Applicants Adrian Gilbert et al.	
Filing Date February 16, 2001	**Group Art Unit** ~~1614~~ 1646

INFORMATION DISCLOSURE CITATION
(Use several sheets if necessary)

U.S. PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate
~~—~~	~~US 09/355,909~~	~~7/22/99~~	~~Strominger et al.~~			
~~—~~	~~US 09/407,347~~	~~9/24/99~~	~~Gad et al.~~			
—	US 09/768,872	1/23/01	Aharoni et al.			
~~—~~	~~US 09/819,629~~	~~3/23/01~~	~~Gad et al.~~			
~~—~~	~~US 09/875,429~~	~~6/5/01~~	~~Yong and Chabot.~~			
~~—~~	~~US 09/884,277~~	~~6/20/01~~	~~Rodriguez and Ure.~~			

FOREIGN PATENT DOCUMENTS

	Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
R	EP 0 388 230	8/22/90	Europe	—	—		
R	EP 0 359 783	11/29/95	Europe	—	—		

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

R	Webb, et al., "Molecular Requirements Involved in Suppression of EAE by Synthetic Basic Copolymers of Amino Acids", Immunochem., 1976, 13, 333-337
	Abramsky, et al., "Effect of a Synthetic Polypeptide (COP-1) on Patients with Multiple Sclerosis and with Acute Disseminated Encephalomyelitis", J. Neurol. Sci., 1977, 31, 433-438
	Teitelbaum, et al., "Suppression of Experimental Allergic Encephalomyelitis in Baboons by Cop 1", Israel J. Med. Sci., 1977, 13, 1038 (Abstract)
	Arnon, et al., "Suppression of EAE in Baboons by a Synthetic Polymer of Amino Acids", Neurol., 1978, 28, 336 (Abstract)
	Sela, et al., "Experimental Allergic Encephalomyelitis" in Menarini Series on Immunopathology, vol. 1, First Symposium of Organ Specific Autoimmunity", Cremona, Italy, June, 1977, (Miescher P.A. ed., Schwabe Co., Basel, 1978), 9-21
	Alvord, et al., "Myelin Basic Protein Treatment of Experimental Allergic Encephalomyelitis in Monkeys", Ann. Neurol., 1979, 6, 469-473
	Keith, et al., "The Effect of COP 1, a Synthetic Polypeptide, on Chronic Relapsing Experimental Allergic Encephalomyelitis in Guinea Pigs" J. Neurol. Sci., 1979, 42, 267-274
	Lando, et al., "Effect of Cyclophosphamide on Suppressor Cell Activity in Mice Unresponsive to EAE", J. Immunol., 1979, 123, 2156-2160 (Abstract)

EXAMINER	DATE CONSIDERED
[signature]	7/10/03

*EXAMINER: Initial if citation considered, whether or not citation is in conform[illegible]

INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	A Aarian Gilbert et al.	
	Filing date February 16, 2001	Group Art Unit 1614/647

OTHER DOCUMENTS *(Including Author, Title, Date, Pertinent Pages, Etc.)*

AC	Matsunaga et al., "Complementation of class II A alleles in the immune response to (Glu-Lys-Tyr) polymers", Yokohama Med. Bull., 1988, 39(1-2):9-19(Abstract)
	De Kruyff et al., "Analysis of T Cell Responses to Poly-L (GluLys) at the Clonal Level. I. Presence of Responsive Clones in Nonresponder Mice", Eur. J. Immunol., 1987, 17 (8): 1115-1120 (Abstract)
	Lai et al., "Complementation of Class II A alleles in the immune response to (GluLysTyr) polymers", Exp. Clin. Immuogenet., 1986, 3(1):38-48 (Abstract)
	Lai, et al., "Monoclonal T cell responses to two epitopes on a single immunogen controlled by two distinct genes", J. Immunol., 1986, 136(10):3799-3804 (Abstract)
	Trannoy et al., "Epitope-specific regulation of the T cell repertoire: carrier recognition in association with I-E or I-A does not influence the restriction of hapten-specific T cells", Eur. J. Immunol., 1985, 15(12):1215-1221 (Abstract)
	Falo et al., "Analysis of antigen presentation by metabolically inactive accessory cells and their isolated membranes", Proc. Natl. Acad. Sci. USA, 1985, 82(19);6647-6651 (Abstract)
	Babu et al., "Ir gene control of T and B Cell Responses to Determinants in (Glu Lys Ala) Terpolymer", J. Immunogenet., 1984, 11(3-4): 251-254
	Babu et al., "Reevaluation of response patterns of nonresponder mice to GLPhe polymers:, Immunogen., 1983, 18(1):97-100 (Abstract)
	Herzenberg et al., "Lack of immune response gene control for induction of epitope specific suppression by TGAL antigen", Nature, 1982, 295: 329-331 (Abstract)
	Baxevanis et al., "Genetic Control of T-Cell Proliferative Responses to Poly ($Glu^{40}Ala^{60}$) and Poly ($Glu^{51}Lys^{34}Tyr^{15}$): Subregion-Specific Inhibition of the Responses with Monoclonal Ia Antibodies", Immunogenetics, 1980, 11: 617-628
	Maurer et al., "Interpretation of immune responses of mice to poly(Glu55Lys37Leu8) and the terpolymers poly (Glu55Lys37Leu8) and poly (Glu56Lys37Ser7)", Clin. Immunol. Immunopathol., 1980, 15(3):34-356 (Abstract)
	Ju et al., "Idiotypic analysis of antibodies against the terpolymer L-glutamic acid 60-L-alanine30-L-tyr sine10 (GAT). IV. Induction of CGAT idiotype following immunization with various synthetic polymers containing glutamic acid and tyrosine", Eur. J. Immunol., 1979, 9(7): 553-560 (Abstract)
	Schwartz et al., "Gene complementation in the T lymphocyte proliferative response to poly (Glu57Lys38Tyr5): Evidence for effects of polymer handling and gene dosage", J. Immunol., 1979, 123(1):272-278 (Abstract)

EXAMINER	DATE CONSIDERED
	12-20-07

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 | Department of Commerce, Patent and Trademark Office | No. 0023-A | Serial No. 09/788,131

INFORMATION DISCLOSURE CITATION
(Use several sheets if necessary)

Applicants: Adrian Gilbert et al.
Filing Date: February 16, 2001
Group Art Unit: ~~1614~~ 1644

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate
AD	US	5,554,372	9/10/96	Hunter et al.			
	US	5,621,052	4/22/97	McLean et al.			
	US	5,734,034	3/31/98	Bishwajit et al.			
	US	5,886,156	3/23/99	McLean et al.			
	US	09/476,077	1/20/00				
	US	09/621,052	7/20/02				
	US	09/734,034					
	US	09/734,034					

OIPE AUG 05 2002 PATENT & TRADEMARK OFFICE

RECEIVED AUG 07 2002 TECH CENTER 1600/2900

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
AD	WO	92/02543	2/20/92	Europe				
	WO	94/03488	2/17/94	US				
	WO	94/26767	11/24/94	US				
	WO	95/26980	10/12/95	US				
	WO	95/33491	11/30/95	US				
	WO	01/58478	7/26/01	US				
	WO	01/91793	12/3/01	US				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

AD	Henry, Celia M., "Special Delivery", Chem. and Eng. News, Sept. 18, 2000, 49-54
	Cohen, "Fundamental Immunology", Systemic Autoimmunity, 5th Ed., 1999, 1083
	Fridkis-Hareli et al., "Binding of random copolymers of three amino acids to class II MHC molecules", Intl. Immunol., 1999, 11(5):633-641
	Li, et al., "Glatiramer acetate blocks the activation of THP-1 cells by interferon-γ", Eur. J. Pharmacol., 1998, 342: 303-310
	Zisman, et al., "Dichotomy between the T and the B cellepitopes of the synthetic polypeptide (T, G)-A--L", Eur. J. Immunol., 1994, 24(10):2497-2505 (Abstract)
	Deeb, et al., "Comparison of Freund's and Ribi adjuvants for inducing antibodies to the synthetic antigen (TG)-AL in rabbits", J. Immunol. Methods, 1992, 152(1): 105-113 (Abstract)
	Zisman et al., "Direct Binding of a synthetic multichain polypeptide to class II Major Histocompatibility Complex Molecules on Antigen-Presenting Cells and stimulation of a specific T-cell line require processing of the polypeptide", Proc. Natl. Acad. Sci. USA, 1991, 88(21):9732-9742 (Abstract)

EXAMINER: Ann DeLuna | DATE CONSIDERED: 12-20-02

*EXAMINER: Initial if citation considered, whether or not citation is in confo